# What's New in Aureomycin and Other Antibiotics

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ANTIBIOTICS, or, more properly, chemotherapeutics, have developed with great rapidity in the few years of their existence. For each anti-infective agent which has received clinical trial and may be deemed worthy of discussion in a brief review of this sort, hundreds have been tried and discarded as lacking in certain desirable qualities. Many others are at present in various stages of development, and newer and more potent drugs will surely appear.

In spite of the availability of chemotherapeutic drugs active against most bacteria and rickettsiae and several viruses, exact etiological diagnosis has become increasingly important. While keeping in mind the treatment of the sick individual as a whole, the physician must clearly realize that he is treating an infection due to a specific pathogenic micro-organism and not merely a pathologic process. Thus the best treatment of pneumonia due to pneumococci differs from that of pneumonia due to M. tuberculosis or psittacosis virus. Likewise pyelonephritis due to Staphylococcus aureus must be treated quite differently from that due to A. aerogenes. Assiduous

search for the etiological agent must be paramount in the proper management of any infectious process.

### AUREOMYCIN

Aureomycin[14] is derived from *Streptomyces aureofaciens*, so-called because of its golden-yellow color. At present available commercially is the hydrochloride salt for oral use. The same purified salt will undoubtedly soon be introduced generally for intravenous administration. In addition, an ophthalmic ointment can be obtained for topical use.

*Clinical Pharmacology.* Aureomycin is absorbed rather slowly from the gastrointestinal tract. Although measurable amounts are detected in the serum after one hour, peak absorption is usually reached in two to six hours. Measurable blood levels may persist for eight to 12 hours after a single oral dose of 1 gm.[4] If oral administration of 1 gm. doses is continued at four- to six-hour intervals, gradual accumulation of aureomycin in the body occurs and serum concentrations in excess of 10 micrograms per milliliter of serum may be found after several days (Table 1).

Following the intravenous administration of 100 mg. an immediate peak serum concentration, usually in excess of that following the initial oral dose of 1 gm. is attained, followed by a gradual decline over a period of six to eight hours.[5] If oral and intravenous routes of administration are combined, immediate high serum levels are achieved and main-

## TABLE I
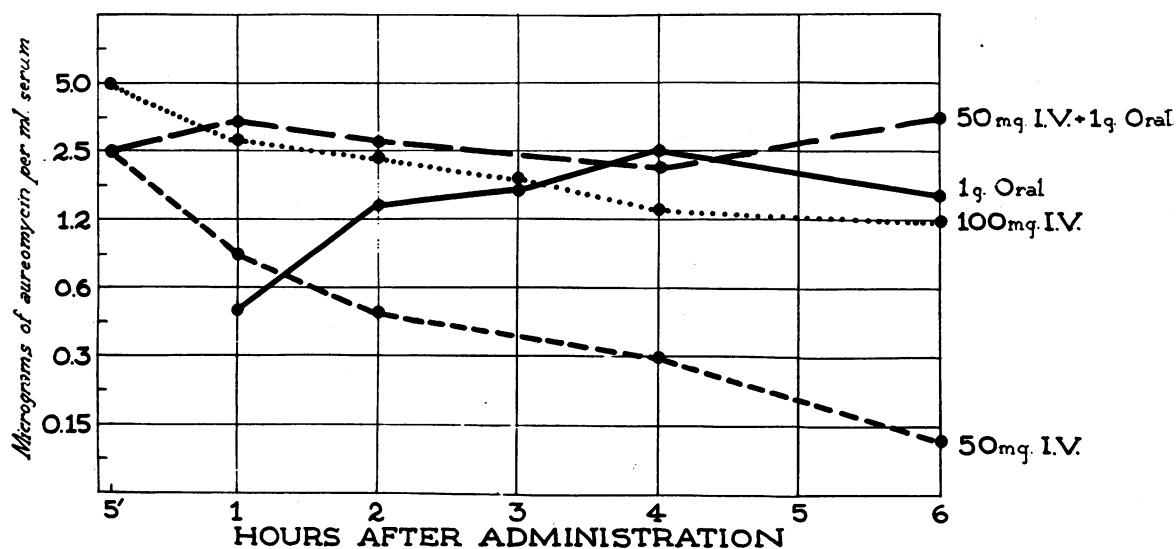


Graph illustrating average serum concentrations of aureomycin following various intravenous and oral doses.

tained. The optimum serum concentrations of aureomycin for the treatment of various infections is not known.

Intramuscular administration of aureomycin is both painful and inefficient, since only minimal serum levels are observed.[4] Aerosolization is followed in some instances by systemic absorption.[5]

Aureomycin appears in most body fluids,[5] although usually after a delay of many hours. Measurable concentrations may be detectable in the pleural fluid, joint fluid, and cerebrospinal fluid after more than 24 hours of administration. Aureomycin appears quickly in the bile and urine. It has been detected in gastric contents eight hours after an oral dose.

Aureomycin is excreted slowly and irregularly in the urine. Urine concentrations in excess of 1 mg. per cc. may be observed occasionally. Urinary excretion may continue for 24 hours following a single intravenous dose of 100 mg. of the drug.[5]

*Anti-Infective Spectrum.* Aureomycin is active *in vitro* against a wide variety of Gram-positive and Gram-negative bacteria[5] as illustrated in Table 2, as well as L. icterohemorrhagica and Borrelia recurrentis.[21] In addition, *in vivo* activity has been demonstrated against the rickettsiae of the typhus, Rocky Mountain spotted fever, scrub typhus, and Q fever groups, as well as the viruses of psittacosis, lymphopathia venereum,[49, 2] and primary atypical pneumonia.[16] This activity has been confirmed in almost all instances by successful clinical trial.*

*Toxicity.* Aureomycin has been demonstrated to have little toxicity for animals. In man the only significant toxic effect has been the occurrence of nausea with or without vomiting in over half the patients receiving 1 gm. doses every four or six hours.[6] This has been avoided, whenever necessary, by resorting to intravenous administration. The nausea may subside spontaneously in spite of continued therapy, or may be partly alleviated by the use of aluminum hydroxide gels and by the presence of food in the stomach before ingestion of the drug.

*Dosage.* Exact dosage requirements in various infections are not established. One gram every six hours by mouth appears adequate in most infections due to susceptible agents. One-half this dosage will probably prove sufficient in primary atypical pneumonia and urinary tract infections due to highly susceptible bacteria. In severe infections or infections due to relatively resistant pathogens, supplemental intravenous doses of 100 mg. may be given simultaneously with the first few oral doses. If oral administration must be avoided because of nausea or for other reasons, 100 mg. may be administered intravenously every six to eight hours. A convenient plan includes three intravenous doses during the day, supplemented by one oral dose at night.

*Results of Clinical Trial.* Aureomycin has been used in a wide variety of infectious diseases, and

*References: 6-9, 11-13, 18, 19, 25-27, 29, 35, 37, 38, 45, 53, 54.

TABLE 2.—*Response to Aureomycin.*

HIGHLY SENSITIVE ORGANISMS (Most strains less than 0.1 micrograms per ml.) :
  Staphylococcus aureus
  Beta hemolytic streptococcus
  Alpha hemolytic streptococcus
  Streptococcus fecalis
  Diplococcus pneumoniae
  Corynebacterium diphtheriae

MODERATELY SENSITIVE ORGANISMS (Most strains less than 1.0 micrograms per ml.) :
  Escherichia coli
  Aerobacter aerogenes
  Eberthella typhosum
  Salmonella (various types)
  Neisseria meningitidis
  Klebsiella pneumoniae
  Hemophilus influenzae
  Shigella paradysenteriae

RESISTANT ORGANISMS (All strains more than 3.5 micrograms per ml.) :
  Proteus vulgaris
  Pseudomonas aeruginosa

preliminary evaluation of it may now be made. Comparison with penicillin, streptomycin, and chloromycetin must await carefully controlled studies.

In general, results of aureomycin therapy in typhoid fever and salmonella infections have been disappointing.[18, 29, 6, 19] Occasional patients respond in a dramatic fashion, but in the majority of patients only moderate suppressive effects or none at all are the rule. The stool culture may be temporarily rendered negative in the typhoid carrier state, but permanent beneficial effect is exceptional.

Aureomycin appears to be a highly effective agent in the treatment of acute brucellosis.[45, 29, 6, 19] Fever and bacteremia are usually quickly abolished, but relapses may occur in a significant number of patients. Small initial doses, as recommended by Spink,[45] should be used for the first three days of treatment to avoid Herxheimer-like reaction. Treatment must be carried out for ten days to two weeks. Experience in the treatment of chronic brucellosis is too limited to permit evaluation.

As is the case with other chemotherapeutic agents, aureomycin rarely produces permanent sterilization in infections of the urinary tract where severe anatomical abnormalities exist.[18, 33, 6] Most patients without obstruction of the urinary passages respond favorably to aureomycin therapy, with the exception of those in whom the infecting organism is a resistant strain of Ps. aeruginosa or Pr. vulgaris. In almost all cases, regardless of infecting organism or anatomical abnormality, marked suppression of the infection may be expected. Since the development of aureomycin resistance is uncommon, this temporary suppressive effect may be utilized to tide the patient over critical periods of disease in hopes of removing obstructive lesions at a later date.

Aureomycin exerts a beneficial effect on the course of pneumococcal pneumonia,[18, 36] and may be considered an alternative to penicillin in this disease. Results in other types of bacterial pneu-

monia and in lung abscess are as yet impossible to evaluate.

Acute gonorrheal urethritis responds favorably to aureomycin in most cases,[18] but the results appear definitely inferior to those of penicillin. Some types of bacterial meningitis may be amenable to aureomycin therapy,[29] although there is not yet sufficient evidence to permit evaluation.

Preliminary experience in pyogenic infections of the peritoneal cavity is promising[29, 6] as might be expected from an agent active against both Gram-positive and Gram-negative organisms. Limited trial in chancroid lesions likewise warrants further use of this agent. Pyodermia and erysipelas also appear to respond favorably.[29, 6]

Although aureomycin is highly active against streptococcus fecalis *in vitro*, results in the treatment of subacute bacterial endocarditis that is caused by penicillin-resistant strains of this organism have been disappointing. Although cures[29] have been reported, two patients who were treated relapsed after the termination of therapy, although the initial response had been satisfactory.[6]

In view of the experimental evidence of Heilman[21] that aureomycin is highly active against Leptospira icterohemorrhagica, the apparently favorable response in one patient[6] suggests that aureomycin may prove to be the treatment of choice in Weil's disease. Aureomycin has been widely used with success in the treatment of primary atypical pneumonia,[25, 37, 19, 29, 6, 36, 34] although relapses may occasionally be encountered after the discontinuance of therapy. Three patients suffering from psittacosis have responded favorably to treatment[6] with aureomycin after they had not improved under therapy with repository penicillin. Aureomycin appears to have no effect on the course of coccidioidal infection.[6] Preliminary reports suggest that aureomycin exerts a beneficial effect on lymphopathia venereum.[53]

Very favorable results with aureomycin have been reported in the treatment of typhus fever,[38] and of Rocky Mountain spotted fever.[12, 35] Although most patients suffering from Q fever seem to respond well to this drug, failures do occur.[27, 6]

Remaining to be evaluated is the role of aureomycin in the treatment of herpes simplex and herpes zoster. No beneficial effects have been noted in varicella, infectious mononucleosis, erythema multiforme, Hodgkin's disease, acute leukemia, or carcinoma.[6]

The principal activity of aureomycin is bacteriostatic rather than bactericidal. In this respect it is reminiscent of the sulfonamides. The immune mechanism of the host may be of great importance in the final eradication of infection.

## PENICILLIN

Of particular interest as regards penicillin is the development of a repository penicillin-procaine complex with 2 per cent aluminum monostearate which will produce measurable blood levels as long as 120 hours after the injection of 300,000 units.[34] While this is a welcome simplification of the care of the patient receiving penicillin, caution in using this material in severely ill patients is advisable. Although serum levels are prolonged, peak concentrations are generally lower than those following administration of more rapidly absorbed preparations.

Of equal interest is the convincing evidence that beneficial clinical results may be obtained by infrequent intramuscular injections of aqueous solutions of crystalline penicillin.[1, 48] Although serum levels may not persist beyond three to seven hours after administration, significant amounts are present in the tissues for longer periods of time. Furthermore, organisms experimentally exposed for brief periods to concentrations of penicillin which would ultimately be lethal are intoxicated so that multiplication does not occur for several hours after their removal from contact with penicillin.[1] Thus such acute infections as pneumococcal pneumonia respond favorably to between 100,000 and 300,000 units administered every eight to 12 hours. In spite of the feasibility of these short-cuts in many cases, patients who are desperately ill should be treated with very large doses at frequent intervals so that maximal concentrations may diffuse into infected foci as soon as possible.

## STREPTOMYCIN

The development of dihydrostreptomycin has accorded streptomycin a secondary role. The reduced derivative is as effective clinically as streptomycin in all types of infections and is considerably less toxic.[33, 22, 23] Eighth nerve toxicity is occasionally observed also with dihydrostreptomycin, but usually only when the drug is given in large doses and for long periods of time.

While the problem of the acquisition of resistance to streptomycin is far from solved, since organisms resistant to streptomycin are equally resistant to dihydrostreptomycin, certain promising developments have been noted. The simultaneous use of para-aminosalicylic[55] acid, and possibly promizole,[28] appears to inhibit the appearance of resistant strains of tubercle bacilli. Furthermore, recently developed substituted streptomycins have been found to be active *in vitro* against organisms resistant to streptomycin and dihydrostreptomycin. Gram-negative organisms resistant to streptomycin are usually quite susceptible to aureomycin, chloromycetin, or polymyxin.

## CHLORAMPHENICOL (CHLOROMYCETIN)

Chloromycetin was originally derived from *Streptomyces venezuelae*[17] but has more recently been synthesized. Its anti-infective spectrum generally resembles that of aureomycin, although it exhibits considerably less activity against the Gram-positive cocci *in vitro*.[29] Chloromycetin is highly active against most Gram-negative organisms *in vitro* and against the rickettsiae *in vivo*.[39] In addition, activity has been demonstrated against the spirochetes, Bor-

relia recurrentis[44] and Treponema pallidum,[42] although activity against the latter is not great.

Chloromycetin is rapidly absorbed from the gastrointestinal tract and is excreted in the urine. No significant toxic effects have been noted. Initial doses of 50 mg. per kilogram of weight appear to be effective, and the dosage may be reduced after clinical improvement occurs.

Although clinical data on results of treatment with chloromycetin are scanty, good results have been reported in typhus fever,[40] scrub typhus,[41] typhoid fever,[26, 51] primary atypical pneumonia,[36] bacterial pneumonia,[36] gonorrhea,[42] brucellosis,[26, 52] and infections of the urinary tract due to Gram-negative organisms.[10] Chloromycetin appears to be definitely superior to aureomycin in the treatment of typhoid fever,[26] although relapses have been encountered in a significant number of cases.

## POLYMYXIN

The polymyxins, of which there are several, are derived from *B. polymyxia*. Polymyxin A is also known as aerosporin. Polymyxins A, B, and D are cyclic polypeptides. All are extremely active against Gram-negative organisms with the notable exception of Pr. vulgaris and the Neisseriae.[46] Although polymyxin is considerably more bactericidal than streptomycin, aureomycin, and chloromycetin against Gram-negative bacteria,[3] it exerts a significant nephrotoxic effect in animals and human beings which will probably limit its use to desperate infections which are not susceptible to other chemotherapeutic agents.[29] The total daily dose of polymyxin ranges from 3 to 6 mg. per kilogram of weight divided into eight intramuscular injections. Beneficial effects have been observed clinically in pertussis,[47] bacteremias due to Ps. aeruginosa[33] and other bacilli, and urinary tract infections due to susceptible organisms.[29]

## BACITRACIN

Bacitracin[24] is derived from *B. subtilis*. It is active against the Gram-positive cocci, the Neisseriae, the Clostridiae, C. diphtheriae, T. pallidum, and E. histolytica. It is not active against Gram-negative organisms. It is neither absorbed nor inactivated in the gastrointestinal tract, and thus depresses the Gram-positive cocci and Clostridiae when administered orally.[32] It is absorbed following intramuscular injection and is excreted slowly. Severe renal lesions may be observed in mice, rats, and man after intramuscular administration of this drug. Bacitracin manufactured by surface culture[43] appears to be less toxic than that made by deep-vat culture, so that side-effects may be eventually minimized.

Beneficial effects have been reported from the topical use of solutions and ointments containing 10 to 100 units of bacitracin per cc.[31] These infections included furuncles, ulcers, and chronic osteomyelitis. Favorable results were noted in about 70 per cent of "surgical" infections treated with bacitracin administered intramuscularly.[32] Because of its syn-

ergistic action with penicillin against T. pallida, it has been used experimentally in the treatment of syphilis,[15] but it is too early to evaluate the results.

## DISCUSSION

While laboratory and clinical studies on these and other antibiotics have gone on at a bewildering pace, the approach has been principally the empirical one of trial and error. Lagging behind have been investigations into the mechanisms of action of chemotherapeutic agents. Although the principle of metabolic competition was first established in regard to the sulfonamides by Woods,[50] only fragmentary evidence is available to explain the action of penicillin and streptomycin. This subject has been ably reviewed by Goldstein.[20] A new era in chemotherapy will appear when drugs are designed specifically to interfere with the vital metabolic functions of the microorganism and, perhaps, the neoplastic cell.

Drs. Henry B. Bruyn, Jr., and Gordon Meiklejohn collaborated in the clinical and pharmacological studies on aureomycin.

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## QUESTIONS AND ANSWERS

DR. BRAINERD: I have two questions on chronic brucellosis. One is: "What is the effect of aureomycin on chronic brucellosis?" The other is: "Why is chronic brucellosis more resistant to therapy than acute brucellosis?"

I don't know for certain what the effect of aureomycin is in chronic brucellosis. A number of cases have been treated but not followed a long enough period of time to tell. I think unquestionably, in many cases there is some effect. Whether it is lasting or not, I think is a very crucial question that time alone will settle.

*Question:* "Rectal administration of capsules of aureomycin has been suggested. Is this effective?"

We have not completed the studies on rectal administration. It would not be surprising that it is absorbed from the rectum. However, the pH of the solution is 2.5. This is exceedingly irritating. If is buffered, it may deteriorate rapidly. These are practical objections to rectal administration. However, they may be surmountable.

*Question:* "To what other antibiotic in addition to streptomycin is Friedlander's bacillus susceptible?"

It is susceptible to aureomycin, chloromycetin and polymyxin.

*Question:* "Have there been reports of anaphylactic reactions to penicillin?"

Yes, there have. They are exceedingly rare. Most reactions, however, are not acute or serious, but merely a nuisance, often resembling serum sickness.

*Question:* "Are there any antibiotics of value against coccidioidal infections?"

There is one antibiotic which is effective against mycotic organisms. It is an actidione which is still in the early experimental stage. It has been used some in coccidioidal infections with some suggestive beneficial results in dogs. Its toxic effects in man are not fully worked out. However, it is of considerable promise in mycotic infections in general.

*Question:* "Is it safe to give aureomycin at the patient's home?"

Yes, I would say it lends itself particularly to administration at home, since the only toxic effect of any consequence is nausea and vomiting, and this is rarely serious. It could be given by mouth, which is a great advantage.

*Question:* "Has aureomycin been used in the treatment of Reiter's disease, and if so, with what results?"

Finland reported one case of apparent Reiter's disease which he felt was benefited to some degree by aureomycin. I have treated one patient—I was not certain what he had was Reiter's disease—without any effect. There is some animal evidence which would suggest that there is some activity against the organism.

*Question:* Does aureomycin act by producing basodilatation?

I think that, by and large, the physiological effects of all the antibiotics are almost nil. Their activity is, of course, quite demonstrable in the test tube where there can be no physiological effect other than the action on the affecting organism. However, that does not minimize the importance of the immune mechanism of the body. In the final abolition of pathogens from the body, all chemotherapeutic agents are probably principally bacteriostatic rather than bactericidal, and the immune mechanism of the body is very important in the eradication of infection.